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Molecular events in the induction of a nonresponsive state in interleukin 2-producing helper T-lymphocyte clones.

Jenkins MK, Pardoll DM, Mizuguchi J, Chused TM, Schwartz RH.

Exposure of normal interleukin 2 (IL-2)-producing helper T-cell clones to antigen and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-treated antigen-presenting cells results in proliferative unresponsiveness to subsequent stimulation with antigen and normal antigen-presenting cells. In the present study, we have examined the molecular events that accompany the induction of this unresponsive state. T cells stimulated in this manner failed to produce IL-2, but interleukin 3, interferon-gamma, and IL-2 receptors were partially induced and T-cell receptor beta mRNA was fully induced. Although T-cell unresponsiveness correlated with an IL-2 production defect, addition of IL-2 during the induction phase failed to prevent development of the unresponsive state. The critical biochemical event appeared to be an increase in intracellular calcium. Removal of calcium from the medium prevented induction of the unresponsive state, whereas addition of the calcium ionophore ionomycin induced unresponsiveness as well as all of the related partial activation events. Thus, an increase in intracellular calcium under nonmitogenic conditions appears to initiate an alternative activation program that prevents the T cell from producing IL-2 in response to subsequent normal activation signals. The significance of this in vitro model for tolerance induction in vivo is discussed.

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1: J Exp Med 1987 Feb 1;165(2):302-19

Antigen presentation by chemically modified splenocytes induces antigen-specific T cell unresponsiveness in vitro and in vivo.

Jenkins MK, Schwartz RH.

We investigated the antigen specificity and presentation requirements for inactivation of T lymphocytes in vitro and in vivo. In vitro studies revealed that splenocytes treated with the crosslinker 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (ECDI) and soluble antigen fragments failed to stimulate significant proliferation by normal pigeon cytochrome c-specific T cell clones, suggesting that the chemical treatment inactivated full antigen presentation function. However, T cell clones exposed to ECDI-treated splenocytes and antigen in vitro were rendered unresponsive for at least 8 d to subsequent antigen stimulation with normal presenting cells. As predicted by the in vitro results, specific T cell unresponsiveness was also induced in vivo in B10.A mice injected intravenously with B10.A, but not B10.A(4R), splenocytes coupled with pigeon cytochrome c via ECDI. The antigen and MHC specificity of the induction of this T cell unresponsiveness in vitro and in vivo was identical to that required for T cell activation. These results suggest that nonmitogenic T cell recognition of antigen/MHC on ECDI-modified APCs results in the functional inactivation of T cell clones.

PMID: 3029267 [PubMed - indexed for MEDLINE]

1: J Immunol 1987 Jun 1;138(11):3704-12 Related Articles, Links

Stimulation of normal inducer T cell clones with antigen presented by purified Ia molecules in planar lipid membranes: specific induction of a long-lived state of proliferative nonresponsiveness.

Quill H, Schwartz RH.

Culture of normal inducer T cell clones with antigen and purified Ek beta:Ek alpha incorporated into planar lipid membranes resulted in specific T cell activation as determined by cell volume increase and IL 3 production. However, in contrast to results obtained with T cell hybridomas, antigen presentation by planar membranes did not induce measurable IL 2 production, and proliferative responses were not detected. Rather, recognition of only Ek beta:Ek alpha and antigen resulted in the specific induction of a long-lived state of proliferative nonresponsiveness to subsequent stimulation by conventional APC and antigen. Induction of nonresponsiveness required protein synthesis, and was not simply due to the absence of IL 2. The antigen-nonresponsive cells could respond to either PMA plus ionomycin or IL 2, and they expressed normal levels of surface antigen-receptor molecules. These results demonstrate that recognition by normal T cell clones of antigen and Ia molecules in the absence of other accessory cell molecules and signals results in a prolonged state of proliferative nonresponsiveness, possibly similar to a state of T cell tolerance in vivo.

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